8-24-19

JAMA 2019 Aug 13; 322:514

Does the Amount of Dietary Gluten in Early Life Increase Risk for Celiac Disease?

Yes, the amount seems to matter, especially in the first 2 years of life, in genetically at-risk children.

Whether the amount of dietary gluten intake in early life contributes to the risk for developing celiac disease (CD) is unknown. In a prospective, international study, researchers examined this possible association in 6605 children carrying HLA antigen genotypes associated with CD. They measured gluten intake at 6, 9, and 12 months and biannually until age 5 years, and screened for CD (via serum sampling for tissue transglutaminase autoantibodies) at age 2 years and annually until age 5 years (median follow-up, 9 years).

Eighteen percent of children developed persistent autoantibodies (at median age of 3 years), and 7% developed biopsy-proven CD. The peak age for each outcome was between 2 and 3 years. Gluten intake in the first 5 years (especially in the first 2 years) was associated with increased risk for seroconversion and CD. Risk increased with each 1-g increase in gluten ingested per day. In children aged <2 years, ingesting >2 g gluten daily (similar to a piece of bread) was associated with a 49% increased risk for autoimmunity and a 75% increased risk for CD compared with ingesting <2 g daily. The highest risk for developing autoantibodies and CD was in children with the genotype HLA DR3-DQ2. Other risk factors included female sex, Swedish residence, and family history of CD.

COMMENT: In this high-risk population, the amount of gluten ingested early in life was associated with risk for CD. As editorialists comment, additional factors must also contribute to the prevalence of CD because countries with high gluten intake do not necessarily have a high CD prevalence. Nonetheless, for children with genetic risk for CD, limiting gluten intake in early life is warranted, while assuring that they still consume adequate fiber and nutritional foods.

CITATION(S): Andrén Aronsson C et al. Association of gluten intake during the first 5 years of life with incidence of celiac disease autoimmunity and celiac disease among children at increased risk. *JAMA* 2019 Aug 13; 322:514. (https://doi.org/10.1001/jama.2019.10329)

Leonard MM and Fasano A. Gluten and celiac disease risk: Is it just a matter of quantity? *JAMA* 2019 Aug 13; 322:510. (https://doi.org/10.1001/jama.2019.9678)

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J Clin Endocrinol Metab 2019 Aug 1; 104:3576.

Is High Dietary Calcium Intake Associated with Better Bone Density?

Prospectively collected observational data showed no association between dietary calcium and bone-mineral density.

Clinicians often assume that in postmenopausal women with osteopenia, higher intake of dietary calcium will mitigate declining bone-mineral density (BMD). To examine this assumption, researchers studied nearly 700 osteopenic postmenopausal women (age, >65) who comprised the placebo group of a randomized bisphosphonate trial. BMD was measured at baseline and at 6 years, and serial assessments of dietary calcium (through food-frequency questionnaires) were obtained. Calcium supplementation was not encouraged, but participants were provided with moderate-dose vitamin D supplements. Daily calcium intake averaged 469 mg in the lowest quintile and 1361 mg in the highest quintile and changed only minimally over time.

At baseline, BMD was similar across all quintiles of calcium intake. At 6 years, gradual decline in BMD was virtually identical in all quintiles. Moreover, across quintiles of calcium intake, researchers noted no significant differences or changes in total body bone-mineral content and no differences in fracture rates. All analyses were adjusted for numerous potentially confounding variables.

COMMENT: Although this study was not a randomized trial of different amounts of dietary calcium, it provides fairly compelling evidence that high intake of dietary calcium does not protect against bone loss in older osteopenic women. As the authors explain, "bone is insulated from the effects of variation in calcium intake" through homeostatic mechanisms that involve parathyroid hormone and vitamin D. On a related note, a recent meta-analysis showed that calcium supplementation did not lower fracture rates in community-dwelling adults (NEJM JW Gen Med Feb 15 2018 and *JAMA* 2017; 318:2466).

CITATION(S): Bristow SM et al. Dietary calcium intake and bone loss over 6 years in osteopenic postmenopausal women. *J Clin Endocrinol Metab* 2019 Aug 1; 104:3576. (https://doi.org/10.1210/jc.2019-00111)

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Lancet Diabetes Endocrinol 2019 Jul 25; S2213-8587(19)30189-5

Just How Effective and Safe Is Testosterone Therapy in Women?

Review and meta-analysis confirm efficacy for women with bothersome low sexual desire, but conclusions about long term safety can't yet be drawn.

Although some clinicians manage bothersome low sexual desire by administering testosterone (T), no formulation specifically for women is available in most countries, including the U.S. Thus, researchers conducted a systematic review and meta-analysis of randomized, controlled trials of T in women. The study focused transdermal patches releasing 300 µg T daily (resulting in blood T levels at the upper end of the premenopausal range) or nontransdermal formulations at

doses achieving blood T levels close to those attained with the patch. Of the 36 trials (8480 participants), most were 12 to 24 weeks in length and the longest duration was 2 years.

Compared with placebo (or a comparator such as menopausal estrogen with or without progestin), T significantly enhanced sexuality outcomes, including event frequency, desire, pleasure, arousal, orgasm, and self-image in postmenopausal women affected by bothersome low sexual desire. Although transdermal T did not alter serum lipid levels, oral T increased LDL-cholesterol while reducing total and HDL-cholesterol as well as triglycerides. Although T was associated with weight gain and increased reports of acne and hair growth, it did not appear to cause serious adverse events.

COMMENT: Although this report did not yield evidence that T negatively affects cardiovascular, breast, or endometrial outcomes, the short-term nature of the trials do not allow conclusions to be drawn about T's long-term safety. I agree in principal with the editorialist that this meta-analysis supports use of transdermal T for menopausal women with bothersome low sexual desire. However, until formulations and doses specific for women become available, I remain reluctant to prescribe T for this indication.

CITATION(S): Islam RM et al. Safety and efficacy of testosterone for women: A systematic review and meta-analysis of randomised controlled trial data. *Lancet Diabetes Endocrinol* 2019 Jul 25; S2213-8587(19)30189-5; [e-pub]. (https://doi.org/10.1016/S2213-8587(19)30189-5)

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Lancet Child Adolesc Health 2019 Aug 13

Frequent Social Media Use Linked to Psychological Distress in Teens

Cyberbullying and inadequate sleep explained these associations in girls, and to a lesser degree in boys.

Studies of the effects of social media use on teens' mental health have shown mixed results, and most have not followed teens over time. These researchers analyzed data from a longitudinal study in England that followed 12,866 teens from age 13 to 16 years with a series of surveys on social media use and psychological well-being.

"Very frequent" social media use (>3 times per day) was common and increased from age 13 to 16 (from 34% to 62% in boys, and 51% to 75% in girls). Compared with teens who used social media <1 time per week, girls with very frequent social media use were 31% more likely to have psychological distress at age 14 to 15 and boys were 67% more likely. Girls with persistently high social media use had lower well-being, life satisfaction, and happiness, and more anxiety. In girls, cyberbullying, poor sleep quality, and low physical activity accounted for most of the association between social media use and psychological distress and well-being, whereas in boys these factors accounted for only a small amount.

COMMENT: This study provides solid evidence of a link between frequent social media use and worse psychological health in teens. Social media use should be discussed at tween and teen well visits, to encourage strategies such as keeping devices out of bedrooms, using "nightshift" or "do not disturb" settings, or turning off Wi-Fi at night. Cyberbullying can be addressed through school curricula (parents can ask schools to use a new digital citizenship curriculum https://www.commonsense.org/education/digital-citizenship) and by parent–teen conversations about upsetting content children may see online. Finally, activities such as face-to-face time with friends, sports, or clubs might help avoid boredom-induced social media checking.

CITATION(S): Viner RM et al. Roles of cyberbullying, sleep, and physical activity in mediating the effects of social media use on mental health and wellbeing among young people in England: A secondary analysis of longitudinal data. *Lancet Child Adolesc Health* 2019 Aug 13; [e-pub]. (https://doi.org/10.1016/S2352-4642(19)30186-5)

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JAMA Neurol 2019 Jul 14

Frequent Social, Mental Activity Tied to Lower Dementia Risk

Cognitive activities throughout the lifespan and social activities in later life were associated with lower risk.

Stimulating mental and social activities over a lifetime are associated with lower risk for developing dementia, according to a *JAMA Neurology* study.

Roughly 1600 older adults (mean age, 80) free of dementia at baseline completed questionnaires on their frequency of cognitive activities in early, mid, and late life and social activities in late life (e.g., reading, volunteering, eating at restaurants, traveling, visiting friends and family). This information, along with years of education, was used to construct a cognitive reserve score.

Over a mean of 6 years' follow-up, 24% of participants developed dementia. After multivariable adjustment, participants in the highest tertile of cognitive reserve scores had a 39% lower risk for dementia diagnosis than those in the lowest tertile. The risk reduction was significant even in participants with high Alzheimer disease and vascular pathologies.

The authors conclude: "Our findings suggest that accumulative educational and mentally stimulating activities enhancing [cognitive reserve] throughout life might be a feasible strategy to prevent dementia."

COMMENT — NEUROLOGY: *Jennifer Rose V. Molano, MD*

Participating in cognitive and social activities throughout the lifespan may decrease dementia risk, even in the presence of Alzheimer disease and vascular pathologies on autopsy. Cognitive activities during nearly the entire lifespan that were queried in the study included reading, writing letters, and visiting the library. Encouraging patients to challenge themselves with novel activities, in addition to exercise and a healthy diet as has been shown elsewhere (NEJM JW Neurol Oct 2019 and *JAMA* 2019; 322:430), may enhance cognitive reserve and modify dementia risk.

CITATION(S): Xu H et al. Association of lifespan cognitive reserve indicator with dementia risk in the presence of brain pathologies. *JAMA Neurol* 2019 Jul 14; [e-pub]. (https://doi.org/10.1001/jamaneurol.2019.2455)

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.Ann Intern Med 2019 Aug 20; 171:248

Do SGLT-2 Inhibitors Cause Severe UTIs?

Urinary tract infections were not more common in patients who took sodium–glucose cotransporter-2 inhibitors.

Sodium—glucose cotransporter-2 (SGLT-2) inhibitors (e.g., canagliflozin [Invokana], dapagliflozin [Farxiga], empagliflozin [Jardiance]) inhibit glucose reabsorption in renal tubules and increase urinary glucose excretion. Some reports, including meta-analyses of randomized trials, suggest that this effect might be associated with excess risk for urinary tract infections (UTIs). Since 2015, the U.S. FDA has required SGLT-2 inhibitors' prescribing information to carry a warning about risk for severe UTIs.

Investigators used two large U.S. insurance databases to conduct a propensity-adjusted analysis comparing SGLT-2 inhibitors with dipeptidyl peptidase-4 (DPP-4) inhibitors or glucagon-like peptide-1 (GLP-1) receptor agonists in >235,000 patients. Compared with DPP-4 inhibitors and GLP-1 agonists, SGLT-2 inhibitors were not associated with excess risk for severe UTIs (defined as hospitalization for UTI, sepsis with UTI, or pyelonephritis) or for outpatient UTIs.

COMMENT: SGLT-2 inhibitors' positive effects on cardiovascular and renal outcomes in diabetic patients with cardiovascular disease make them attractive agents for this patient population (NEJM JW Gen Med Aug 1 2017 and *N Engl J Med* 2017; 377:644 and NEJM JW Gen Med May 15 2019 and *N Engl J Med* 2019; 380:2295). Although the current study reassures us about the safety of this medication class related to severe UTIs, recent reports suggest excess risk for other adverse outcomes (e.g., amputations, ketoacidosis, Fournier gangrene) with this drug class. Also, this analysis included only U.S. insured patients and excluded patients with histories of UTIs and those at high risk for UTIs, possibly limiting generalizability of the findings.

CITATION(S): Dave CV et al. Sodium–glucose cotransporter-2 inhibitors and the risk for severe urinary tract infections: A population-based cohort study. *Ann Intern Med* 2019 Aug 20; 171:248. (https://doi.org/10.7326/M18-3136)

Filion KB and Yu OH. Sodium–glucose cotransporter-2 inhibitors and severe urinary tract infections: Reassuring real-world evidence. *Ann Intern Med* 2019 Aug 20; 171:289. (https://doi.org/10.7326/M19-1950)

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Unraveling the Safety Profile of Proton-Pump Inhibitors

John R. Saltzman, MD and David J. Bjorkman, MD, MSPH (HSA), SM (Epid.)

A large randomized trial has shown no association between PPI use and most of the adverse outcomes noted in observational studies.

Proton-pump inhibitors (PPIs) provide important clinical benefits for many patients. However, observational studies have suggested an association between PPI use and a variety of adverse events, including dementia, osteoporosis, bone fractures, micronutrient deficiencies, pneumonia, spontaneous bacterial peritonitis, kidney disease, and enteric infections. We have observed that some patients with documented indications for PPIs have stopped the drugs on their own after hearing media reports about frightening potential side effects such as dementia; other patients have discontinued them on the advice of their physicians. As an illustration, we provide the following example — a composite of several cases seen in our gastroenterology practices:

A 60-year-old woman with a history of a peptic ulcer needed a nonsteroidal anti-inflammatory drug (NSAID) to manage her osteoarthritis. Her physician recommended that she take a PPI along with her NSAID, and she did so for several months; her arthritic pain improved, and she had no gastrointestinal symptoms. However, she read about a possible link between PPIs and dementia and was particularly worried because she had a family history of Alzheimer disease. She decided to discontinue the PPI. Two weeks later she presented with upper gastrointestinal bleeding, and urgent endoscopy was performed to treat a bleeding gastric ulcer.

The postulated adverse effects of PPIs generally have been noted in retrospective analyses of databases created for other purposes. But now, a rigorously conducted, prospective, randomized trial has cast doubt on the credibility of most of those claims (NEJM JW Gastroenterol Aug 9 2019; [e-pub] and *Gastroenterology*2019; 157:403). Nearly 18,000 patients with stable cardiovascular disease were randomly assigned to receive either a PPI (pantoprazole, 40 mg once daily) or placebo. During average follow-up of 3 years, there were no associations between PPI therapy and nearly all safety outcomes (dementia, bone fracture, new diagnoses of diabetes mellitus, chronic kidney disease, pneumonia, chronic obstructive pulmonary disease, gastric atrophy, cancer overall, and cancers of specific primary sites). The one exception was a small, barely significant association with enteric infections (1.4% with pantoprazole vs. 1.0% with placebo). For *Clostridium difficile*specifically, there were only nine cases in the pantoprazole group and four cases in the placebo group, a nonsignificant difference.

Methodologic limitations of observational studies are often ignored or poorly explained by the lay media, and many physicians who prescribe PPIs may not be familiar with the strengths and weaknesses of the relevant literature on PPI side effects. However, even before the aforementioned randomized trial was published, there was reason to doubt whether the reported associations between PPIs and the publicized adverse effects were causal. In a 2017 review of observational

studies that showed these associations, researchers applied standard epidemiologic criteria for causation (Hill criteria). They concluded that these studies were prone to residual confounding (i.e., a high likelihood that links between PPIs and adverse events were mediated by other factors) and that the evidence for causality was weak.

Additionally, observational studies can vary in their rigor and conclusions; the alleged association between PPI use and dementia provides an instructive example. The report that initially attracted media attention in 2016 was a retrospective study drawn from an insurance claims database, and the researchers were unable to control for key confounding variables (NEJM JW Gen Med Jun 15 2016 and *JAMA Neurol* 2016; 73:410). Subsequently in 2017 and 2018, methodologically stronger observational studies — which included prospective assessments of cognitive impairment and dementia and more-rigorous controlling for potentially confounding factors — failed to corroborate the PPI–dementia link (NEJM JW Gen Med Sep 15 2017 and *Am J Gastroenterol* 2017; 112:1802 and *Gastroenterology* 2017; 153:971; NEJM JW Gen Med Mar 15 2018 and *J Am Geriatr Soc* 2018; 66:247; JW Gen Med Nov 15 2017 and *J Am Geriatr Soc* 2017; 65:1969).

Wrap-up: In our view, the recently published randomized trial provides considerable reassurance that PPIs are relatively safe drugs. Clinicians should reassure patients with legitimate indications for PPIs that the benefits are likely to outweigh the mostly unsubstantiated claims of serious adverse effects. If there are as-yet unidentified side effects of PPIs, the risks are very low. PPIs are an important cornerstone in managing gastroesophageal reflux disease, in treating patients with gastroduodenal ulceration, and in reducing the probability of upper gastrointestinal bleeding from aspirin or NSAIDs in high-risk patients. Of course, inappropriate use of PPIs should be avoided, as there is no threshold of acceptable risk for a drug that is not indicated.

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Clin Gastroenterol Hepatol 2019 Aug 5

False-Positive Multitarget Stool DNA Tests: What Are the Risks for Subsequent Cancers?

The incidence of lung and digestive tract cancers was comparable to expected incidence based on population rates.

The multitarget stool DNA (mt-sDNA) test is a highly sensitive, noninvasive colorectal cancer screening option for average-risk individuals. However, there is uncertainty about whether patients with a positive stool DNA test result but negative colonoscopy are at increased risk for cancer and therefore require additional scrutiny and evaluation.

To explore this issue, investigators conducted a retrospective, multicenter, cohort study of 1216 patients with negative screening colonoscopies (no neoplasia or only nonadvanced adenomas) and either negative (concordant) or positive (discordant) mt-sDNA results. The researchers compared the incidence of subsequent aerodigestive cancers with expected incidence based on Surveillance, Epidemiology, and End Results (SEER) data.

Results were as follows:

- During a median follow-up of 5.3 years, the number of cancer cases diagnosed among the 205 patients in the discordant group was similar to the expected number, based on SEER data (5 and 6 cases, respectively; risk ratio, 0.8; *P*=0.599).
- During a median follow-up of 5.4 years, the number of cancer cases diagnosed among the 1101 patients in the concordant group was significantly lower than the expected number, based on SEER data (11 vs. 30 cases; RR, 0.4; *P*=0.0008).
- The adjusted risk ratio for cancers was not significantly greater in the discordant group than in the concordant group (RR, 2.2; *P*=0.151).

COMMENT: An apparently positive mt-sDNA test result can generate a great deal of anxiety for patients and providers alike. This study provides some reassurance that asymptomatic individuals with positive mt-sDNA results and negative

colonoscopy results do not require additional assessment for other cancers. A fundamental caveat is that the colonoscopy must be a true negative, meaning that the bowel preparation quality is adequate and that the examination is complete and meticulous, preferably by an endoscopist with high adenoma detection rate. The specificity of mt-sDNA decreases with advancing age, thus the discordance should occur less frequently if the test is offered primarily to patients 50 to 65 years old.

Note to readers: At the time we reviewed this paper, its publisher noted that it was not in final form and that subsequent changes might be made.

CITATION(S): Berger BM et al. Low incidence of aerodigestive cancers in patients with negative results from colonoscopies, regardless of findings from multi-target stool DNA tests. *Clin Gastroenterol Hepatol* 2019 Aug 5; [e-pub]. (https://doi.org/10.1016/j.cgh.2019.07.057)

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Ann Rheum Dis 2019 Aug; 78:1114.

Optimal Duration of Antibiotic Use in Septic Arthritis

This study supports a 2-week course in conjunction with surgery.

The standard of care for patients with septic arthritis has long been 3 to 6 weeks of antibiotics, usually following surgical drainage, but recommendations on duration of treatment and use of parenteral versus oral therapy have not been based on solid evidence. In this nonblinded study, Swiss investigators aimed to define the optimal duration and route of antibiotic therapy. They randomized 154 nonimmunocompromised patients with native-joint septic arthritis, including 99 patients with hand/wrist arthritis, to receive 2 or 4 weeks of antibiotics after surgical drainage, with a switch from intravenous to oral therapy at clinicians' discretion.

In an intent-to-treat analysis of the entire study population, complete microbiological cure occurred in nearly all patients — 97% of those in the 4-week group and 99% of those in the 2-week group. In the subgroup of 99 hand/wrist patients, these rates were 95% and 98%, respectively. However, the investigators could not draw definitive conclusions about the subgroup of 55 patients with involvement of larger joints because of small sample size. Median duration of intravenous therapy was 2 days in the 4-week group and 1 day in the 2-week group.

COMMENT: Outcomes were similar for antibiotic durations of 2 or 4 weeks. The results support shorter courses of antibiotics — particularly for septic hand/wrist arthritis — after surgical drainage and reinforce the use of bioavailable oral antibiotics over parenteral therapy.

CITATION(S): Gjika E et al. Two weeks versus four weeks of antibiotic therapy after surgical drainage for native joint bacterial arthritis: A prospective, randomised, non-inferiority trial. *Ann Rheum Dis* 2019 Aug; 78:1114. (https://doi.org/10.1136/annrheumdis-2019-215116)

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